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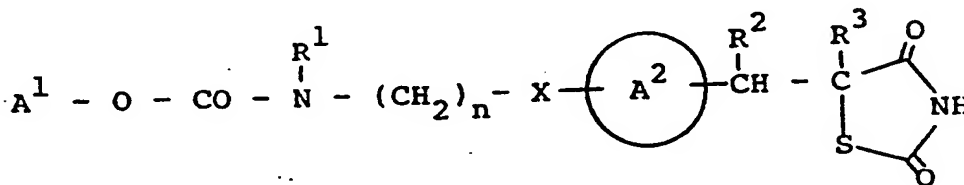
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/GB91/01834 (22) International Filing Date: 18 October 1991 (18.10.91) (30) Priority data: 9023583.9 30 October 1990 (30.10.90) GB (71) Applicant (for all designated States except US): BEECHAM GROUP PLC [GB/GB]; SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : HAIGH, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). BELL, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).		(74) Agent: RUTTER, Kieth; SmithKline Beecham, Corporate Patents, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>

(54) Title: THIAZOLIDINE DIONE DERIVATIVES

(I)

(57) Abstract

A compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein: A¹ represents an alkyl group, a substituted or unsubstituted aryl group or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted; A² represents a benzene ring having in total up to three optional substituents; R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; or A¹ together with R¹ represents substituted or unsubstituted C₂₋₃ polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group; R² and R³ each represent hydrogen, or R² and R³ together represent a bond; X represents O or S; and n represents an integer in the range of from 2 to 6; a process for preparing such a compound, a composition comprising such a compound and the use of such a compound or composition in medicine.

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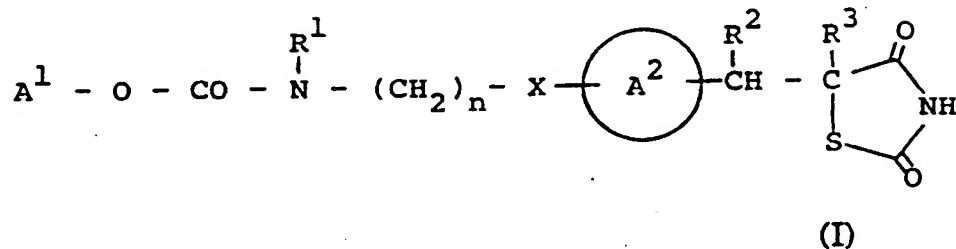
This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

10 thiazolidinedione derivatives which are disclosed as having hypoglycaemic and hypolipidaemic activity. Chem. Pharm. Bull 30 (10) 3580-3600 also relates to certain thiazolidinedione derivatives having hypoglycaemic and hypolipidaemic activities.

20

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

25 Accordingly, the present invention provides a compound of formula (I):



35 or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein: A¹ represents an alkyl group, a substituted or unsubstituted aryl group or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

A² represents a benzene ring having in total up to three optional substituents;

R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl or the aryl moiety may be substituted or

5 unsubstituted, or a substituted or unsubstituted aryl group;

or A¹ together with R¹ represents substituted or unsubstituted C₂₋₃ polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted

10 or unsubstituted phenylene group;

R² and R³ each represent hydrogen, or R² and R³ together represent a bond;

X represents O or S; and

n represents an integer in the range of from 2 to 6.

15

When A¹ represents an aryl group, the aryl group is suitably an unsubstituted aryl group.

20 When A¹ represents an aralkyl group, the aralkyl group is suitably an aralkyl group of formula aryl(CH₂)_m, wherein m is 1, 2, 3 or 4, preferably 1 or 2; preferably the aryl moiety is unsubstituted.

Suitably, A¹ represents an alkyl group, a substituted or unsubstituted aryl group or an aralkyl group wherein the alkylene or the aryl moiety
25 may be substituted or unsubstituted; and R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl or the aryl moiety may be substituted or unsubstituted; or a substituted or unsubstituted aryl group;

30 Suitably, A¹ together with R¹ represents substituted or unsubstituted C₂₋₃ polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

35

Favoured substituted or unsubstituted C₂₋₃-polymethylene groups include substituted or unsubstituted ethylene groups.

Suitable optional substituents for the C₂₋₃-polymethylene group, includes C₁₋₆-alkyl and optionally substituted phenyl groups or adjacent substituents together with the carbon atoms to which they are attached form an optionally substituted phenylene group.

5

Optional substituents for the phenyl group are those mentioned hereinafter in relation to aryl groups.

Optional substituents for the phenylene group are selected from: halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy and alkylcarbonyl groups.

15

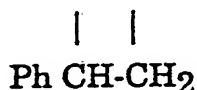
Preferably the phenylene group is unsubstituted.

Examples of A¹ include phenyl, benzyl and 2-phenylethyl.

Examples of R¹ include methyl, phenyl and 2-hydroxy-2-phenyl ethyl.

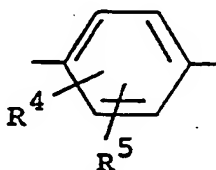
Examples of substituted or unsubstituted C₂₋₃ polymethylene groups represented by A¹ together with R¹ include 1,2-phenylene and a moiety of formula:

25



Suitable substituents for the moiety A² include halogen, substituted or unsubstituted alkyl or alkoxy.

Favourably, A² represents a moiety of formula (a):



(a)

35

wherein R⁴ and R⁵ each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R⁴ and R⁵ each independently represent hydrogen, halogen, alkyl or alkoxy.

Preferably, R⁴ and R⁵ each represent hydrogen.

5

Suitably, R¹ represents hydrogen, alkyl, aryl, especially phenyl, acyl, especially acetyl, or benzyl.

Preferably, R¹ represents a methyl group.

10

Suitably, R² and R³ each represent hydrogen.

In one aspect, X represents sulphur. Preferably, X represents oxygen.

15 Suitably, n represents an integer 2, 3 or 4, notably 2 or 3 and especially 2.

As indicated above a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

20

When used herein the term 'aryl' or the term 'ar' as used for example in 'aralkyl' includes phenyl and naphthyl, preferably phenyl, optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxyalkyl, hydroxy, amino, nitro, cyano, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

30

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

35

When used herein the terms 'alkyl' (whether used alone or as part of other groups such as aralkyl) or 'alk' (as used for example in 'alkoxy') relate to alkyl groups having straight or branched carbon chains, containing up to 12 carbon atoms.

Suitable alkyl groups are C₁₋₁₂ alkyl groups, especially C₁₋₆ alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

- 5 Suitable optional substituents for any alkyl group include those mentioned hereinbefore in relation to aryl.

When used herein the term 'acyl' includes alkylcarbonyl or arylcarbonyl groups.

10

Suitable pharmaceutically acceptable salts include salts of the thiazolidinedione moiety, and, where appropriate, salts of carboxy groups.

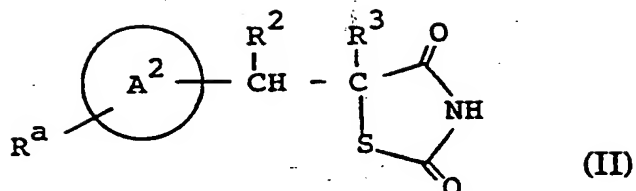
- 15 Suitable pharmaceutically acceptable salts of the thiazolidinedione moiety include metal salts especially alkali metal salts such as the lithium, sodium and potassium salts, for example a sodium salt.

- 20 Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, 25 or with procaine, dibenzylpiperidine, N-benzyl-b-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine or quinoline.

- 30 Suitable pharmaceutically acceptable solvates include hydrates.

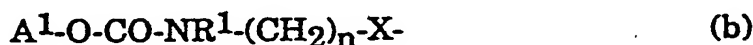
- In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a 35 pharmaceutically acceptable hydrate thereof, which process comprises reacting a compound of formula (II):

5



wherein R^2 , R^3 and A^2 are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of formula (b):

10



wherein A^1 , R^1 , X and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (b) and thereafter, if required, carrying out one or more of the following optional steps:

- (i) converting a compound of formula (I) into a further compound of formula (I);
- (ii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

For compounds of formula (I) other than those wherein A^1 together with R^1 represents a substituted or unsubstituted C_{2-3} -polymethylene group, R^a suitably represents $R^{1a}HN-(CH_2)_n-X-$ wherein X and n are as defined in relation to formula (I) and R^{1a} represents hydrogen, alkyl, acyl or aralkyl, wherein the alkyl or aryl moiety may be substituted or unsubstituted, or substituted or unsubstituted aryl.

Suitably, when R^a is $R^{1a}HN-(CH_2)_n-X-$, an appropriate reagent capable of converting R^a into a moiety (b) is a compound of formula (III):



wherein A^3 is alkyl, substituted or unsubstituted aryl or aralkyl substituted or unsubstituted in the aryl moiety and L^1 represents a leaving group.

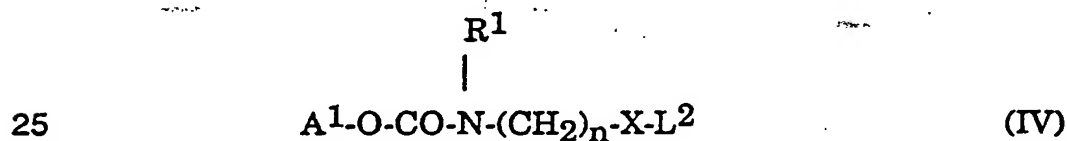
A suitable leaving group L^1 includes a halogen atom, preferably a chlorine or bromine atom, or an alkoxy group.

5 The reaction between the compound of formula (II) and the appropriate reagent may be carried out under conditions suitable to the particular compound of formula (II) and the reagent chosen; thus for example the abovementioned reaction between a compound of formula (II) wherein R^a represents $R^{1a}HN-(CH_2)_n-X$ and the compound of formula (III), may be carried out in any suitable solvent, for example dimethylformamide, at an
10 elevated temperature in the range of from 0 to 100°C, preferably 0 to 80°C for example 80°C; optionally in the presence of a suitable base, for example triethylamine.

15 Preferably, R^a represents $-XH$, wherein X is defined in relation to formula (I).

Alternatively, R^a represents a leaving group or atom, such as a halogen atom, preferably a fluorine atom.

20 When R^a is $-XH$, a particularly appropriate reagent is a compound of formula (IV);



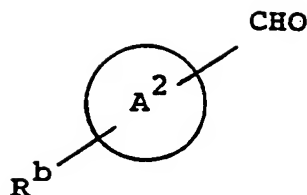
wherein A^1 , R^1 , X and n are as defined in relation to formula (I) and L^2 represents a leaving group such as a mesyl or tosyl group.

30 The reaction between the compounds of formulae (II) and (IV) may be carried out in any suitable aprotic solvent, for example dimethylformamide, at any temperature providing a suitable rate of formation of the required product, conveniently at an elevated temperature, suitably in the range of from 60°C to 100°C for example
35 80°C; preferably the reaction is carried out in the presence of a base, such as sodium hydride and in an inert atmosphere, for example nitrogen.

A compound of formula (II) may be prepared by reacting a compound of

formula (V):

5



(V)

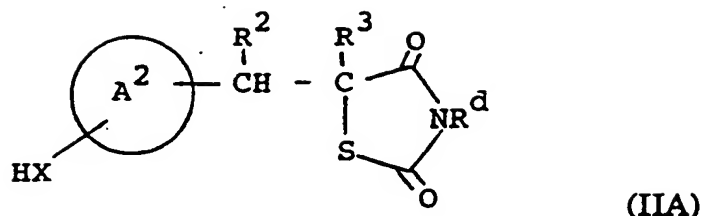
- 10 wherein A^2 is as defined in relation to formula (I) and R^b represents R^a or a protected form thereof, with 2,4-thiazolidinedione or a protected form thereof; and thereafter, if required, reducing a compound of formula (II) wherein R^2 together with R^3 represent a bond to give a compound of formula (II) wherein R^2 and R^3 each represent hydrogen and/or removing
15 any protecting group and/or converting one group R^a into another group R^a .

The reaction between the compound of formula (V) and 2,4-thiazolidinedione will of course be carried out under conditions
20 suitable to the nature of the compound of formula (V), in general the reaction being carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of
25 formula (V) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus. The piperidinium acetate or benzoate may be prepared in-situ from piperidine and either acetic acid or benzoic acid.

- 30 For compounds of formula (II) wherein R^a is HX -, R^b suitably represents a protected form of R^a , for example a group R^cX - where R^c is a benzyl group.

The interconversion of one group R^a into another may be effected by any
35 suitable procedure: for example a compound of formula (II) wherein R^a is $R^{1a}HN-(CH_2)_n-X$ may be prepared from the corresponding compound of formula (II) wherein R^a is $-XH$; thus the appropriate conversion may be carried out by coupling a compound of formula (IIA):

5



- 10 wherein R^2 , R^3 , A^2 and X are as defined in relation to formula (I) and R^d is hydrogen or a nitrogen protecting group, with a compound of formula (VI):



15

wherein R^{1a} and n are as defined above and R^e is hydrogen or a nitrogen protecting group, in the presence of a suitable coupling agent; and thereafter, if required, carrying out one or more of the following optional steps:

20

- (i) reducing a compound of formula (II) wherein R^2 and R^3 together represent a bond, to a compound of formula (II) wherein R^2 and R^3 each represent hydrogen;
- 25 (ii) removing any nitrogen protecting group.

A suitable coupling agent for the coupling reaction between the compound of formula (IIA) and (VI) is provided by diethylazodicarboxylate and triphenylphosphine. The coupling reaction may be carried out in any suitable solvent at a low to medium temperature, for example in tetrahydrofuran at a temperature in the range of between 0 and 60°C.

30

A compound of formula (IV) may be prepared by suitable conversion of a compound formula (VII):

35



- 10 -

wherein A^1 , R^1 , X and n are as defined in relating to formula (I); for example when L^2 in (IV) represents a mesyl or tosyl group, the suitable conversion may be effected by mesylation or tosylation, as appropriate, in an inert solvent such as dichloromethane at any temperature providing a suitable rate of formation of the required product, conveniently at room temperature or lower, for example at 0°C , and preferably in the presence of a base such as triethylamine; alternatively the reaction may be carried out in a basic solvent such as pyridine under similar reaction conditions.

A compound of formula (VII) wherein A^1 represents alkyl, substituted or unsubstituted aryl or an aralkyl group substituted or unsubstituted in the aryl or alkyl moiety and R^1 represents R^{1a} , as defined above, may be prepared by reacting a compound of the hereinbefore defined formula (III) with a compound of formula (VIII):

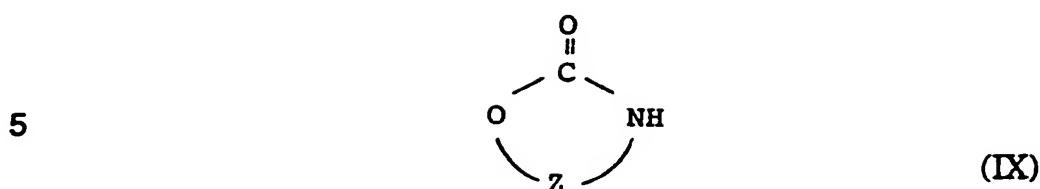


wherein R^{1a} , X and n are as defined above.

The reaction between the compounds of formulae (III) and (VIII) may be carried out under conventional acylation conditions: the reaction is conveniently effected in a biphasic solvent system such as water/chloroform or in water only in the presence of a base such as sodium carbonate, alternatively the reaction may be carried out in an inert solvent such as methylene dichloride in the presence of a base such as pyridine; the reaction proceeding at a temperature providing a convenient rate of formation of the required product, suitably at room temperature or lower, for example at 0°C .

A compound of formula (VII) wherein A^1 together with R^1 represents a substituted or unsubstituted C_{2-3} -polymethylene group, as defined in relation to formula (I), may be prepared by reacting a compound of formula (IX):

- 11 -



wherein Z represents the substituted or unsubstituted C₂₋₃-polymethylene group as defined in relation to formula (I), with a
 10 compound of formula (X):



wherein X and n are as defined in relation to formula (I), L³ represents a
 15 leaving group, preferably a bromine atom, and R^f represents hydrogen or a protecting group.

The reaction between compounds of formulae (IX) and (X) may be carried
 out in any suitable aprotic solvent, such as dimethylformamide, at any
 20 temperature providing a suitable rate of formation of the required
 product, suitably at a temperature in the range of from 0° to 100°C, for
 example 80°C and preferably in the presence of a base such as potassium
 carbonate or sodium hydride.

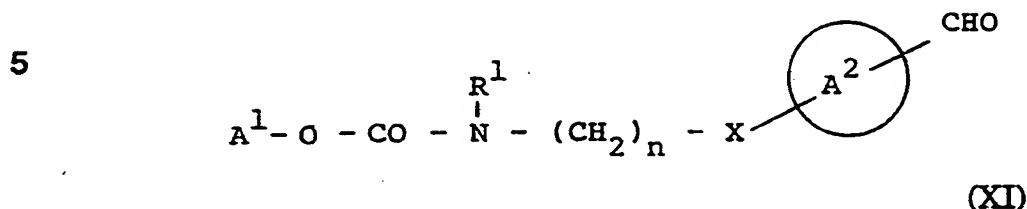
25 The compounds of formula (VII) wherein A¹ together with R¹ represent a
 substituted or unsubstituted C₂₋₃-polymethylene group may also be
 prepared according to methods disclosed in J. Heterocyclic Chem., 1988,
 25, 1601.

30 The compounds of formula (III), (V) and (VIII) are either known
 commercially available compounds or are prepared using methods
 analogous to those used to prepare known compounds, for example
 methods disclosed in Advanced Organic Chemistry, J. March, McGraw
 Hill or, especially for compounds of formula (III), Angew. Chemie, Int. Ed.,
 35 Eng., 1987, p894.

A compound of formula (I), or a tautomeric form thereof, and/or a
 pharmaceutically acceptable salt thereof and/or a pharmaceutically

- 12 -

acceptable solvate thereof, may also be prepared by reacting a compound of formula (XI):



10 wherein R^1 , A^1 , A^2 , X and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more of the following optional steps:

15 (i) converting a compound of formula (I) into a further compound of formula (I);

(ii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

20 The reaction between the compound of formula (XI) and 2,4-thiazolidinedione will of course be carried out under conditions suitable to the nature of the compound of formula (XI), in general the reaction being carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and

25 preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate. Favourably, in the reaction between the compound of formula (XI) and 2,4-thiazolidinedione, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark apparatus. The piperidinium acetate or benzoate may be

30 prepared in-situ from piperidine and either acetic acid or benzoic acid.

A compound of formula (XI) may be prepared from a compound of formula (V), or a protected form thereof, wherein R^b represents R^a , by reaction with an appropriate reagent capable of converting R^a to the above defined

35 moiety (b).

Suitable values for R^a in compound (V) include those described above in relation to the compound of formula (II). Appropriate reagents are also

described above in relation to formula (II).

Suitable reaction conditions for the reaction of the compound of formula (V) and the appropriate reagent include those described above in relation
5 to the preparation of compound (II) with the said appropriate reagent.

Suitable protected forms of compounds of formula (V) include those wherein the aldehyde group is protected. Suitable protecting groups are those used conventionally in the art. It has been found convenient to
10 protect the aldehyde group by reducing it to a hydroxymethyl group, deprotection is conveniently effected by oxidation back to the aldehyde. Suitable reducing agents are conventional agents such as complex metal hydride reducing agents, such as lithium aluminium hydride. Suitable
oxidising agents are conventional oxidising agents such as $\text{Mn}^{\text{IV}}\text{O}_2$.

15 In one preferred aspect for preparing compounds of formula (XI), R^b in compound (V) may represent a leaving group or atom, especially a fluorine atom; when R^b represents a leaving group or atom, preferably a fluorine atom, a particularly appropriate reagent is a compound of the
20 abovedefined formula (VII).

The reaction between the compounds of formulae (V) and (VII) may be carried out under any suitable conditions, for example in a solvent such as dimethylformamide or dimethylsulphoxide at an elevated temperature for
25 example in the range of from 60 to 150°C, suitably in the presence of a base such as sodium hydride, sodium hydroxide or potassium carbonate and preferably in an inert atmosphere such as hydrogen.

Compounds of formula (V) wherein R^b is a protected form of R^a may be
30 prepared from the corresponding compound of formula (V) wherein R^b is R^a .

The compounds of formula (V) wherein R^b is hydroxyl or fluorine are known compounds or compounds prepared by methods analogous to those
35 used to prepare known compounds, for example 4-fluorobenzaldehyde and 4-hydroxybenzaldehyde are known commercially available compounds. The compounds of formula (V) wherein R^b is -SH are prepared according to methods disclosed in Beilstein 8.I.533.

The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes the following conversions:

- 5 (a) reducing a compound of formula (I) wherein R^2 and R^3 together represent a bond, to a compound of formula (I) wherein R^2 and R^3 each represent hydrogen;
- (b) converting one group R^1 into another group R^1 ; and
- 10 (c) converting one moiety $A^1-O.CO.NR^1-$ into another moiety $A^1-O.CO.NR^1-$.

The conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure.

15

A suitable reduction method for the abovementioned conversion (a) includes catalytic reduction or the use of a metal/solvent reducing system.

20

Suitable catalysts for use in the catalytic reduction are palladium on carbon catalysts, preferably a 10% palladium on charcoal catalyst; the reduction being carried out in a solvent, for example dioxan, suitably at ambient temperature and if required at an elevated pressure, for example

25 90 or 900 psi.

Suitable metal/solvent reducing systems include magnesium in methanol.

The abovementioned reduction of a compound of formula (II) wherein R^2 and R^3 together represent a bond to a compound of formula (II) wherein R^2 and R^3 each represent hydrogen, may be carried out under analogous conditions to those referred to above in conversion (a) of the compound of formula (I).

30

35 In the abovementioned conversion (b), suitable conversions of one group R^1 into another group R^1 includes for example converting a group R^1 which represents hydrogen into a group R^1 which represents an alkyl group.

The conversion of a compound of formula (I) wherein R^1 represents hydrogen into a compound of formula (I) wherein R^1 represents alkyl may be carried out using any appropriate conventional alkylation procedure, such as by treating an appropriately protected compound of formula (I) with an alkyl halide for example an alkyl iodide.

One example of conversion (c) is that wherein the moiety $A^1-O.CO.NR^1$ wherein A^1 represents alkyl, substituted or unsubstituted aryl or aralkyl as defined in relation to formula (I) and R^1 is an aralkyl group having a hydroxy group substituent on the alkyl moiety, then the conversion provides a moiety of formula $A^1-O.CO.NR'$ wherein A^1 together with R^1 represents a substituted C_{2-3} polymethylene group wherein substituents are selected from alkyl, aryl or aralkyl as defined in relation to formula (I); thus when A^1 is benzyl and R^1 is $Ph\ CH(OH)CH_2-$, the conversion provides 5-phenyl-2-oxazolidinon-3-yl; the conversion is effected by heating the appropriate compound of formula (I) in a solvent such as ethanol, in the presence of an acid such as dilute hydrochloric acid.

It will be appreciated that in the abovementioned conversions (a), (b) and (c), any reactive group in the compound of formula (I) would be protected, according to conventional chemical practice, where necessary.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example, a suitable nitrogen protecting group is a benzyl group or a benzyloxycarbonyl group or, especially for the thiazolidinedione nitrogen, a trimethylsilyl group or an allyl group and a suitable hydroxyl protecting group is a benzyl group.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example an N-benzyl group may be prepared by treatment of the appropriate amine with a benzyl halide, such as benzyl bromide, and thereafter when required the benzyl group may be conveniently removed using catalytic hydrogenation.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as

individual isomers using conventional chemical procedures.

Pharmaceutically acceptable salts and/or solvates of the compounds of formula (I) may be prepared according to conventional procedures.

5

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

10 The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

15 Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

20 In a further aspect the present invention also provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

25 As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

30 A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

35

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or

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a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces
5 compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by
10 written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration
15 by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

20 In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

25 Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

Most suitably the composition will be formulated in unit dose form. Such
30 unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or
35 prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically

- 18 -

acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

5 The present invention further provides a method for the treatment of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a
10 hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

15 In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described
20 above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

25 In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be administered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis
30 of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

35 In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate

thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

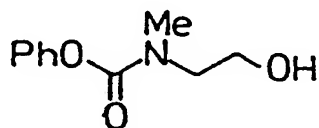
5 The present invention also provides the use of a compound of formula (I),
or a tautomeric form thereof
and/or a pharmaceutically acceptable salt thereof, and/or a
pharmaceutically acceptable solvate thereof, for the manufacture of a
medicament for the treatment and/or prophylaxis of hyperlipidaemia,
hypertension, cardiovascular disease or certain eating disorders.

10

The following Procedures and Examples illustrate the invention but do not limit it in any way.

Procedure 12-(N-Phenoxycarbonyl-N-methylamino)ethanol

5



10 Phenyl chloroformate (20.4g; 16.3ml) was added to a mixture of 2-(N-methylamino)ethanol (12.0g; 13ml) dissolved in saturated sodium carbonate solution (200ml) with stirring and ice cooling. A further quantity of water (100ml) and chloroform (150ml) were added, and the biphasic mixture stirred for 3 hours at 0°C. The layers were separated, and the aqueous layer extracted with chloroform (300ml). The combined
15 organic layers were washed with water (3x300ml) and brine (300ml), dried (MgSO₄) and evaporated. The title compound was obtained as an oil following chromatography on silica gel with 1.5% methanol in dichloromethane as solvent.

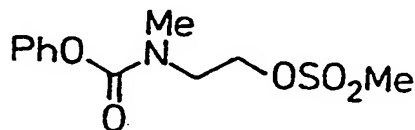
20 ¹H NMR δ (CDCl₃)

The peaks of this spectrum are complicated by the presence of rotational isomers of the carbamate group.

2.50-3.00 (1H, broad apparent d, exchanges with D₂O); 3.15 (3H, br s);
25 3.50 (2H, distorted t); 3.75 (2H, distorted t); 7.00-7.60 (5H, complex).

Procedure 22-(N-Phenoxycarbonyl-N-methylamino)ethanol methanesulphonyl ester

30



35 Methanesulphonyl chloride (3.15g; 2.2ml) was added dropwise to a stirred, ice-cooled mixture of 2-(N-phenoxycarbonyl-N-methylamino)ethanol (4.89g) and triethylamine (3.05g; 4.2ml) in dichloromethane (100ml). The mixture was stirred at 0°C for 1.5 hours, then diluted with

dichloromethane (100ml) and washed with water (3x200ml), brine (200ml), dried (MgSO₄) and evaporated. The title compound, an oil, was used without further purification.

5 ¹H NMR δ (CDCl₃)

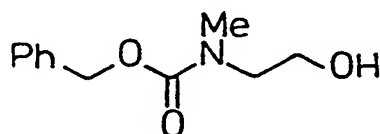
The peaks of this spectrum are complicated by the presence of rotational isomers of the carbamate group.

3.05 (3H, s); 3.17 (3H, apparent d); 3.75 (2H, complex); 4.45 (2H, t);
10 7.10-7.70 (5H, complex).

Procedure 3

2-(N-Benzoyloxycarbonyl-N-methylamino)ethanol

15



20 Benzyl chloroformate (22g; 18.4ml) was added slowly to a vigorously stirred, ice-cooled mixture of 2-(N-methylamino)ethanol (12.0g; 13ml) in saturated sodium carbonate solution (200ml). The mixture was allowed to warm to room temperature and then stirred for an additional 16.5 hours, before being diluted with water (500ml) and extracted with
25 dichloromethane (3x250ml). The combined organic layers were washed with water and brine, dried (MgSO₄) and evaporated. The title compound, an oil, was used without further purification.

¹H NMR δ (CDCl₃)

30

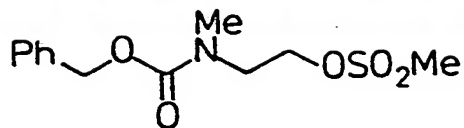
Some peaks in this spectrum are complicated by the presence of rotational isomers of the carbamate group.

2.00-2.90 (1H, br s, exchanges with D₂O); 3.00 (3H, s); 3.42 (2H, distorted t); 3.75 (2H, br t); 5.20 (2H, s); and 7.40 (5H, s).

35

Procedure 42-(N-Benzoyloxycarbonyl-N-methylamino)ethanol methanesulphonyl ester

5



10 Methanesulphonyl chloride (12.88g; 8.7ml) was added slowly to a stirred, ice-cooled solution of 2-(N-benzoyloxycarbonyl-N-methylamino)ethanol (19.47g) in pyridine (200ml). The mixture was stirred at 0°C for 30 minutes, then at room temperature overnight before being diluted with water (1l) and extracted with ethyl acetate (3x300ml). The combined ethyl acetate layers were washed with water (3x300ml), brine (300ml), dried (MgSO₄) and evaporated. The title compound, an oil, was used
15 without further purification.

¹H NMR d (CDCl₃)

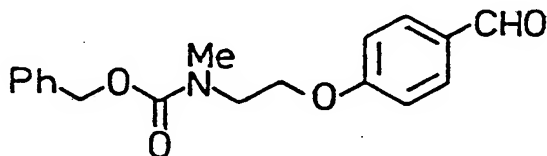
20 Some peaks in this spectrum are complicated by the presence of rotational isomers of the carbamate group.
3.00-3.20 (6H, complex); 3.60 (2H, complex); 4.30 (2H, distorted t); 5.15 (2H, s); and 7.40 (5H, s).

Procedure 5

25

4-[2-(N-Benzoyloxycarbonyl-N-methylamino)ethoxyl]benzaldehyde.

30



2-(N-Benzoyloxycarbonyl-N-methylamino)ethanol methanesulphonyl ester (22.8g) and 4-hydroxybenzaldehyde (10.12g) were reacted together in a manner similar to that described in Example 1. The title compound, an oil, was obtained by chromatography of the crude product on silica gel
35 with 1.5% methanol in dichloromethane as solvent.

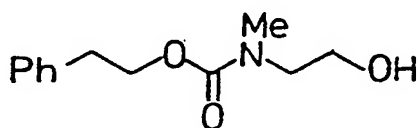
^1H NMR δ (CDCl_3)

This spectrum is complicated by the presence of rotational isomers of the carbamate group.

- 5 3.00 (3H, s); 3.65 (2H, distorted t); 4.15 (2H, br t); 5.05 (2H, s); 6.85 (2H, br d); 7.22 (5H, s); 7.70 (2H, d); and 9.75 (1H, s).

Procedure 6

- 10 2-(N-(2-Phenylethoxy)carbonyl-N-methylamino)ethanol.



15

- (i) : Bis-trichloromethyl carbonate (10g) was dissolved in dichloromethane (200ml) at 0°C under a nitrogen atmosphere. Pyridine (8.07g; 8.25ml) was slowly added, and the resulting solution stirred at 0°C during the careful addition of a solution of 2-phenylethanol (12.48g; 12.2ml) in
20 dichloromethane (20ml total volume). The mixture was allowed to warm to room temperature and the stirring continued for an additional 64.5 hours (tlc showed complete reaction). This reaction mixture, containing impure 2-phenylethyl chloroformate, was used directly in part (ii).

- 25 (ii) : The chloroformate solution (from (i) above) was added slowly over 15 minutes to a stirred, ice-cooled mixture of 2-(N-methylamino)ethanol (7.67g; 8.2ml) and pyridine (16.1g; 16.5ml) in dichloromethane (100ml). The resulting mixture was allowed to warm to room temperature over 4
30 hours, and then diluted with dilute hydrochloric acid (400ml). The layers were separated, and the organic layer was washed with water (3x400ml) and brine (400ml), dried (MgSO_4) and evaporated. The residue was chromatographed on silica gel with 2% methanol in dichloromethane as solvent to afford the title compound as an oil.

- 35 ^1H NMR δ (CDCl_3)

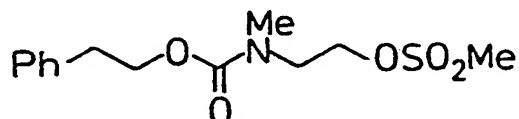
Some peaks in this spectrum are complicated by the presence of rotational isomers of the carbamate group.

2.50 (1H, s exchanges with D₂O); 2.95 (5H, complex); 3.32 (2H, distorted t); 3.65 (2H, br t); 4.30 (2H, t); and 7.30 (5H, s).

5 Procedure 7

2-(N-(2-Phenylethoxy)carbonyl-N-methylamino)ethanolmethanesulphonyl ester.

10



15 The title compound was prepared from 2-(N-(2-Phenylethoxy)carbonyl-N-methylamino)ethanol (5.57g) by a procedure analogous to that described for Procedure 2, and was used in the next stage without further purification.

¹H NMR δ (CDCl₃)

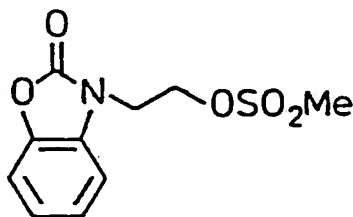
20

Some peaks in this spectrum are complicated by the presence of rotational isomers of the carbamate group. 2.80-3.10 (8H, complex); 3.55 (2H, br t); 4.20 (2H, apparent br s); 4.30 (2H, t); and 7.33 (5H, s).

25 Procedure 8

2-(2-Benzoxazolinon-3-yl)ethanol methanesulphonyl ester.

30



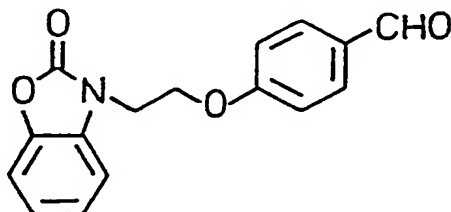
35 The title compound, mp 100-102°C, was prepared from 3-(2-hydroxyethyl)benzoxazolin-2-one (1.79g) by a procedure analogous to that described for Procedure 2, and was used in the next step without further purification.

^1H NMR δ (CDCl_3)

3.05 (3H, s); 4.25 (2H, t); 4.62 (2H, t); and 7.10-7.50 (4H, complex).

5 Procedure 94-[2-(2-Benzoxazolinon-3-yl)ethoxy]benzaldehyde.

10



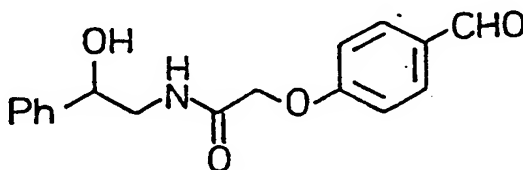
15 A mixture of 2-(2-benzoxazolinon-3-yl)ethanol methanesulphonyl ester (2.36g), potassium carbonate (1.27g), 4-hydroxybenzaldehyde (1.12g) and dry dimethylformamide (100ml) was heated at 80°C with stirring for 17 hours, then allowed to stand at room temperature for 48 hours. The solvent was evaporated and the residue suspended in water (400ml) and
20 extracted with ethyl acetate (3x250ml). The combined organic layers were washed with brine, dried (MgSO_4) and evaporated. The title compound, mp 124-6°C, was purified by recrystallisation from dichloromethane-hexane.

25 ^1H NMR δ (CDCl_3)

4.10-4.50 (4H, complex); 6.95 (2H, d); 7.27 (4H, s); 7.85 (2H, d); and 9.95 (1H, s).

30 Procedure 104-[N-(2-Hydroxy-2-phenylethyl)aminocarbonylmethoxy]benzaldehyde.

35



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(i): Thionyl chloride (79.3g, 48.7ml) was added dropwise to a stirred, ice-cooled suspension of 4-carboxymethoxybenzaldehyde (20g) in dry benzene (200ml) containing pyridine (6ml). The resulting mixture was heated at reflux for 1.5 hours, then cooled and the solvent evaporated.

5 The residue containing impure 4-(dichloromethyl)phenoxyacetyl chloride was used in the next stage of the procedure without further purification.

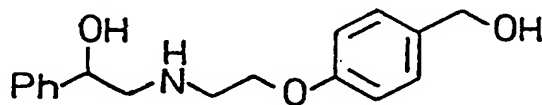
(ii): A solution of 2-amino-1-phenylethanol (15.2g) in dichloromethane (100ml) was added dropwise to an ice-cooled, stirred solution of the acid chloride (part(i): above) in dichloromethane (100ml). Sodium hydroxide solution (10% w/v, 150ml) was added, and the mixture stirred vigorously overnight at room temperature. The mixture was evaporated, the residue dissolved in a mixture of dilute hydrochloric acid (2.5M, 200ml) and methanol (50ml), re-evaporated and then redissolved in sodium hydroxide solution (10% w/v, 200ml). The solution was extracted with ethyl acetate (3x200ml), brine (200ml), dried (MgSO₄) and evaporated. The residue was chromatographed on silica gel with 2% methanol in dichloromethane to afford the title compound.

20 ¹H NMR δ (CDCl₃: DMSO-d₆, 1:1)

3.00-3.60 (2H, complex); 4.55 (2H, s); 4.70 (1H, dd); 5.35 (1H, br s, exchanges with D₂O); 7.02 (2H, d); 7.35 (5H, s); 7.80 (3H, broad d, reduced to 2H, d, on shaking with D₂O); and 9.90 (1H, s).

25 Procedure 11

4-[2-N-(2-Hydroxy-2-phenylethyl)aminoethoxy]benzyl alcohol.



35 A solution of 4-[N-(2-hydroxy-2-phenylethyl)aminocarbonyl-methoxy]benzaldehyde (10.9g) in dry tetrahydrofuran (200ml) was cautiously added to a mechanically stirred, ice-cooled slurry of lithium aluminium hydride (6.94g) in dry tetrahydrofuran (150ml) under a nitrogen atmosphere. The resulting mixture was heated at reflux for 7

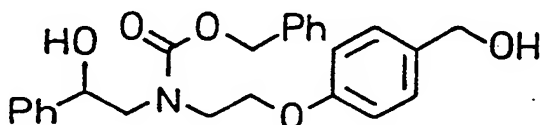
hours and then cooled in ice and cautiously quenched by the addition of water (7ml), sodium hydroxide solution (10% w/v, 7ml) and water (14ml). After being refluxed for a further 30 minutes, the mixture was filtered through a Soxhlet thimble and the residue extracted with refluxing tetrahydrofuran for 3 hours. The solvent was evaporated to afford the title compound as an oil which was used without further purification.

^1H NMR δ (CDCl_3 : $\text{DMSO}-d_6$, 1:1)

3.00 (4H, complex); 3.00-4.50 (3H, broad s, exchanges with D_2O); 4.07 (2H, t); 4.55 (2H, s); 4.77 (1H, dd); 6.90 (2H, d); and 7.35 (7H, complex).

Procedure 12

4-[2-(N-Benzoyloxycarbonyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]benzyl alcohol.



Benzyl chloroformate (14.3g, 12ml) was added dropwise to a vigorously stirred mixture of 4-[2-N-(2-hydroxy-2-phenylethyl)aminoethoxy]benzyl alcohol (8.0g), sodium hydroxide solution (10% w/v, 125ml) and dichloromethane (200ml). After stirring for 30 minutes the phases were separated, the aqueous layer was extracted with dichloromethane (100ml), and the combined organic layers were washed with water (2x100ml), brine (2x100ml), dried (MgSO_4) and evaporated. The residue was chromatographed on silica gel with 4% methanol in dichloromethane as solvent to yield the title compound as a gum.

^1H NMR δ (CDCl_3)

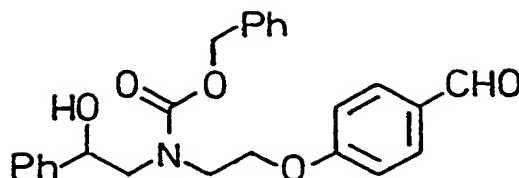
This spectrum is complicated by the presence of rotational isomers of the carbamate group.
2.00 (1H, s, exchanges with D_2O); 3.20-4.30 (7H, complex; reduces to 6H on shaking with D_2O); 4.61 (2H, s); 5.05 (1H, broad apparent singlet);

- 28 -

5.20 (2H, s); and 6.70-7.70 (14H, complex).

Procedure 135 4-[2-(N-Benzoyloxycarbonyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]-benzaldehyde.

10



15 A mixture of 4-[2-(N-benzoyloxycarbonyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]benzyl alcohol (6.3g), manganese (IV) oxide (13.0g) and dichloromethane (150ml) were stirred at room temperature for 24 hours. The mixture was filtered through a Soxhlet thimble and the residue extracted with refluxing dichloromethane for 3 hours. The solvent was evaporated and the resulting gum chromatographed on silica gel with 3% methanol in dichloromethane to afford the title compound as a gum.

20

 ^1H NMR δ (CDCl_3)

This spectrum is complicated by the presence of rotational isomers of the carbamate group.

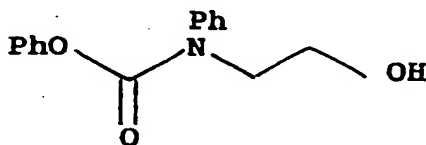
25 3.00 (1H, br s, exchanges with D_2O); 3.40-4.35 (6H, complex); 5.05 (1H, complex); 5.20 (2H, s); 7.00 (2H, complex); 7.40 (10H, complex); 7.85 (2H, d); and 10.00 (1H, s).

Procedure 14

30

2-(N-Phenoxycarbonyl-N-phenylamino)ethanol

35



The title compound, m.p. 124-6°C, was prepared from phenyl chloroformate (15.66g; 12.5ml) and 2-(N-phenylamino)ethanol (13.72g; 12.6ml) by a procedure analogous to that described in Procedure 1, and was used without further purification.

5

¹H NMR δ (CDCl₃)

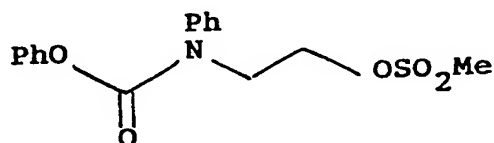
2.40 (1H, br s, exchanges with D₂O); 3.63-3.95 (4H, complex); and 7.00 - 7.55 (10H, complex).

10

Procedure 15

2-(N-Phenoxycarbonyl-N-phenylamino)ethanol methanesulphonyl ester

15



20

The title compound was prepared from 2-(N-Phenoxycarbonyl-N-phenylamino)ethanol (5.14g) by a method analogous to that described in Procedure 2, and was purified by chromatography on silica gel with 1.5% methanol in dichloromethane as solvent. The resulting oil was used directly in the next stage.

25

¹H NMR δ (CDCl₃)

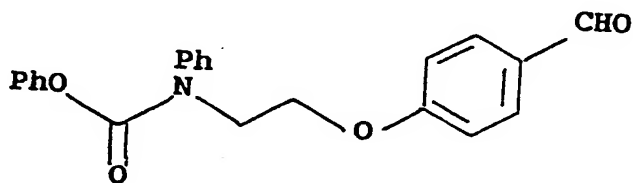
2.95 (3H, s); 4.10 (2H, t); 4.45 (2H, t); and 7.10-7.65 (10H, complex)

30

Procedure 16

4-[2-(N-Phenoxycarbonyl-N-phenylamino)ethoxy]benzaldehyde

35



2-(N-Phenoxycarbonyl-N-phenylamino)ethanol methanesulphonyl ester (5.81g) and 4-hydroxybenzaldehyde (2.08g) were reacted together in a

- 30 -

manner similar to that described in Example 1. The crude reaction product was chromatographed on silica gel with 1.5% methanol in dichloromethane as solvent to afford the title compound as a thick gum.

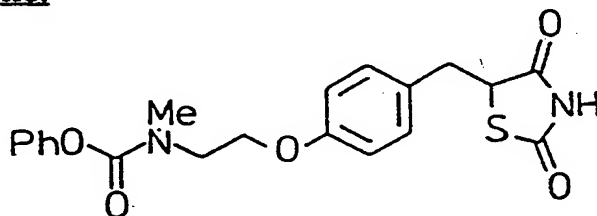
5 ^1H NMR δ (CDCl_3)

4.00 - 4.50 (4H, complex); 6.90 - 7.60 (12H, complex); 7.82 (2H, d); and 9.95 (1H, s).

10 Example 1

5-(4-[2-(N-Phenoxycarbonyl-N-methylamino)ethoxy]benzyl)-2,4-thiazolidinedione.

15



20 5-(4-Hydroxybenzyl)-2,4-thiazolidinedione (5.83g) was dissolved in dry dimethylformamide (100ml) at room temperature. Sodium hydride (60% dispersion in oil; 2.1g) was added portionwise, and the mixture stirred under nitrogen at room temperature for 1 hour. A solution of
25 2-(N-phenoxycarbonyl-N-methylamino)ethanol methanesulphonyl ester (6.78g) in dry dimethylformamide (100ml) was added and the resulting mixture heated at 80°C for 21 hours. After cooling the mixture was diluted with water (1l) and acidified to pH 6.5 with concentrated hydrochloric acid, before being extracted with ethyl acetate (3x400ml). The combined organic layers were washed with water (3x1l) and brine
30 (1l), dried (MgSO_4) and evaporated. The title compound was obtained as a foam (mp $45\text{-}50^\circ\text{C}$) following chromatography on silica gel with 1.5% methanol in dichloromethane as solvent.

^1H NMR δ (DMSO-d_6 ; 120°C)

35

Spectrum is complicated by the presence of rotational isomers of the carbamate group. These coalesce at 120°C .

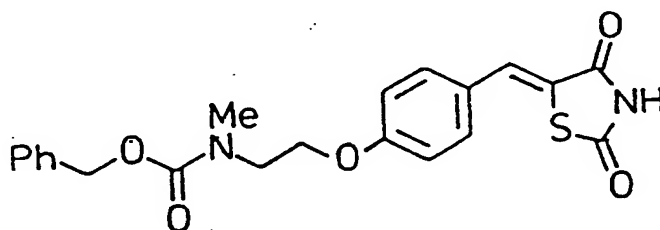
3.05 (3H, s); 3.07 (1H, dd); 3.32 (1H, dd); 3.71 (2H, t); 4.20 (2H, t), 4.75

- 31 -

(1H, dd); 6.85-7.40 (9H, complex); and 11.55 (1H, br s; exchanges with D₂O).

Example 2

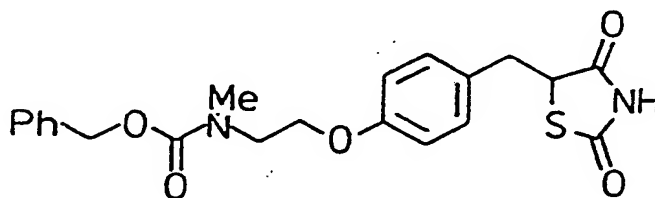
5-(4-[2-(N-Benzoyloxycarbonyl-N-methylamino)ethoxy]-benzylidene)-2,4-thiazolidinedione.



A mixture of 4-[2-(N-benzoyloxycarbonyl-N-methylamino)ethoxy]-benzaldehyde (6.57g), 2,4-thiazolidinedione (2.95g), piperidine (10 drops) and acetic acid (5 drops) were heated at reflux in toluene (400ml) in a Dean and Stark apparatus. After 5 hours at reflux the mixture was allowed to cool to room temperature overnight and then evaporated to dryness. The residue was triturated with diethyl ether for 24 hours and the resulting solid, the title compound, filtered off, washed with ether and dried under vacuum, mp 160-162°C.

¹H NMR δ (CDCl₃/DMSO-d₆; 1:1)

Some peaks in this spectrum are complicated by the presence of rotational isomers of the carbamate group. 3.00 (3H, br s); 3.65 (2H, br t); 4.20 (2H, br t); 5.15 (2H, s); 7.00 (2H, br d); 7.25-7.65 (7H, complex); 7.83 (1H, s); and 12.00 (1H, br s; exchanges with D₂O).

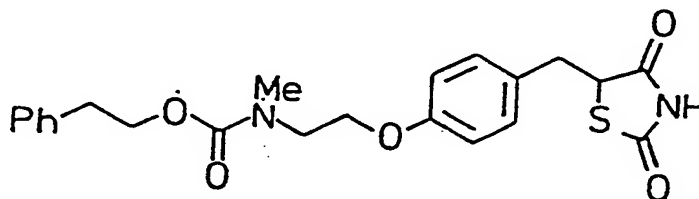
Example 3**5-(4-[2-(N-Benzylloxycarbonyl-N-methylamino)ethoxy]benzyl)-2,4-thiazolidinedione.**

5-(4-[2-(N-Benzylloxycarbonyl-N-methylamino)ethoxy]-benzylidene)-2,4-thiazolidinedione (8.84g) was suspended in dioxan (200ml) and hydrogenated over 10% Palladium-charcoal (8g) at 90 psi overnight. The mixture was filtered through diatomaceous earth, the filter cake thoroughly washed with dioxan, and the combined dioxan solutions evaporated to afford the title compound as a low melting foam.

 ^1H NMR δ (CDCl_3).

This spectrum is complicated by the presence of rotational isomers of the carbamate group.

3.10 (3H, s); 3.00-3.80 (4H, complex); 4.15 (2H, distorted t); 4.52 (1H, dd); 5.23 (2H, s); 6.90 (2H, br d); 7.25 (2H, d); 7.50 (5H, s); and 9.86 (1H, br s).

Example 4**5-(4-[2-(N-(2-Phenylethoxy)carbonyl-N-methylamino)-ethoxy]benzyl)-2,4-thiazolidinedione.**

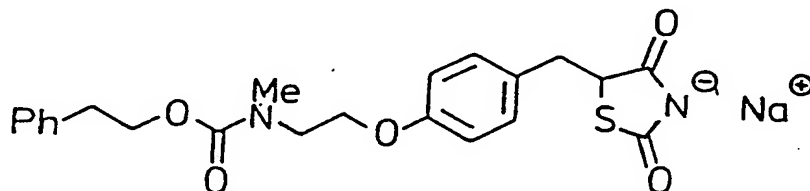
2-(N-(2-Phenylethoxy)carbonyl-N-methylamino)ethanolmethanesulphonyl ester (7.16g) and 5-(4-hydroxybenzyl)-2,4-thiazolidinedione (5.59g) were reacted together in a manner analogous to that described in Example 1. The title compound was obtained as a sticky foam following chromatography on silica gel with 1.5% methanol in dichloromethane as solvent. This material was used directly in salt formation.

¹H NMR δ (CDCl₃).

Some peaks in this spectrum are complicated by the presence of rotational isomers of the carbamate group. 2.80-3.10 (6H, complex); 3.30-3.70 (3H, complex); 3.95 (2H, apparent br s); 4.33 (2H, t); 4.45 (1H, dd); 6.70-7.40 (9H, complex); and 9.50 (1H, br s; exchanges with D₂O).

Example 5

5-(4-[2-(N-(2-Phenylethoxy)carbonyl-N-methylamino)ethoxy]benzyl)-2,4-thiazolidinedione Sodium salt.



Sodium hydride (60% dispersion in oil; 0.48g) was added to a stirred, ice-cooled solution of 5-(4-[2-(N-(2-Phenylethoxy)carbonyl-N-methylamino)ethoxy]benzyl)-2,4-thiazolidinedione (5.00g) in methanol (50ml). The mixture was stirred for 5 minutes at 0°C, and then evaporated under reduced pressure at room temperature. The residue was suspended in dry diethyl ether (200ml) and stirred at room temperature for 5 minutes prior to filtration. The resulting solid, the title compound, was washed thoroughly with dry ether and dried under vacuum at 70°C. The title compound darkens at 235°C, and melts at 246-249°C.

^1H NMR δ (DMSO- d_6 ; 120°C)

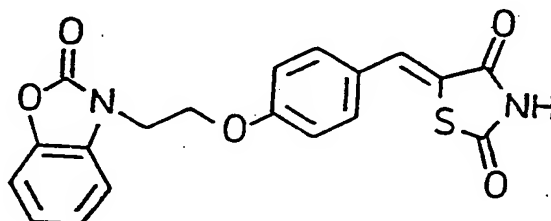
Spectrum is complicated by the presence of rotational isomers of the carbamate group. These coalesce at 120°C.

- 5 2.71 (1H, dd); 2.80-3.00 (5H, complex); 3.36 (1H, dd); 3.52 (2H, t); 4.02 (3H, complex); 4.25 (2H, t); 6.75 (2H, d); 7.05-7.40 (7H; complex).

Example 6

- 10 5-(4-[2-(2-Benzoxazolinon-3-yl)ethoxy]benzylidene)2,4-thiazolidinedione.

15



- 20 A mixture of 4-[2-(2-benzoxazolinon-3-yl)-ethoxy]benzaldehyde (1.89g), 2,4-thiazolidinedione (0.90g), benzoic acid (0.1g) and piperidine (0.1ml) were heated at reflux in toluene (125ml) in a Dean and Stark apparatus. After 3.5 hours at reflux the mixture was allowed to cool and crystallise overnight. The title compound, mp 255-8°C, was filtered off, washed with cold toluene and dried under vacuum.

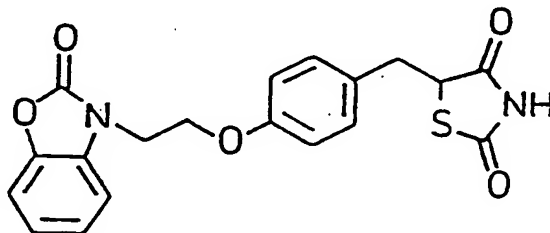
- 25 ^1H NMR δ (CDCl $_3$ /DMSO- d_6 ; 1:1)

4.20-4.60 (4H, complex); 7.00-8.00 (9H, complex); and 12.50 (1H, br, exchanges with D $_2$ O).

- 30 Example 7

5-(4-[2-(2-Benzoxazolinon-3-yl)ethoxy]benzyl)-2,4-thiazolidinedione

35



- 35 -

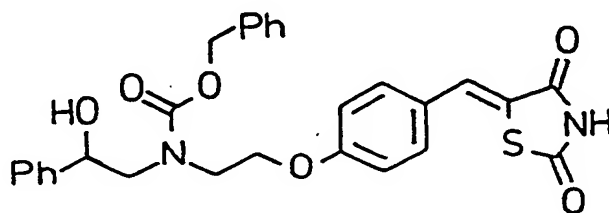
A suspension of 5-(4-[2-(2-benzoxazolinon-3-yl)-ethoxy]-benzylidene)-2,4-thiazolidinedione (2.29g) in dioxan (200ml) was hydrogenated at room temperature and pressure in the presence of 10% palladium-charcoal (2.7g) for 6.75 hours. A further portion of catalyst (2.1g) was added, and the reaction continued for a total of 23 hours. The reaction mixture was filtered through diatomaceous earth, and the solvent evaporated. The resulting gum was recrystallised from dichloromethane-hexane to afford the title compound, mp 157-8°C.

¹H NMR δ (CDCl₃/DMSO-d₆; 1:1)

3.03 (1H, dd); 3.41 (1H, dd); 4.27 (4H, complex); 4.41 (1H, dd); 6.77 (2H, d); 7.00-7.30 (6H, complex); and 11.61 (1H, br, exchanges with D₂O).

Example 8

5-(4-[2-(N-Benzoyloxycarbonyl-N-(2-hydroxy-2-phenyl-ethyl)amino)-ethoxy]benzylidene)-2,4-thiazolidinedione.



The title compound, mp 157-8°C, was prepared from 4-[2-(N-benzoyloxycarbonyl-N-(2-hydroxy-2-phenylethyl)amino)ethoxy]benzaldehyde (5.0g) by a procedure analogous to that described in Example 6.

¹H NMR δ (CDCl₃/DMSO-d₆; 1:1)

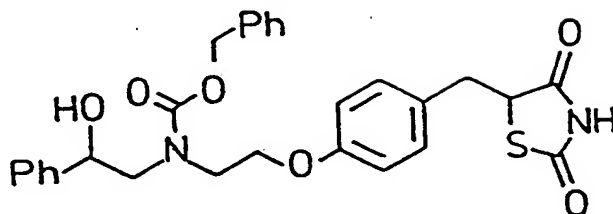
This spectrum is complicated by the presence of rotational isomers of the carbamate group.

3.30-3.70 (4H, complex); 4.10 (2H, complex); 4.75 (1H, apparent broad singlet); 5.05 (2H, apparent d); 5.30 (1H, br s, exchanges with D₂O); 6.20 (1H, broad, exchanges with D₂O); 6.80-7.60 (14H, complex); and 7.68 (1H, s).

Example 9

5 5-(4-[2-(N-Benzylloxycarbonyl-N-(2-hydroxy-2-phenyl-ethyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione.

10



15

5-(4-[2-(N-Benzylloxycarbonyl-N-(2-hydroxy-2-phenyl-ethyl)amino)ethoxy]benzylidene)-2,4-thiazolidinedione (5.0g) was dissolved in dioxan (100ml) and hydrogenated over 10% palladium-charcoal (10g) at 700 psi for 6 hours. The mixture was filtered through diatomaceous earth, the filtercake washed with dioxan (1l), and the combined dioxan layers were evaporated to afford the title compound as a gum which was used in the next step without purification.

20 ^1H NMR δ (CDCl_3)

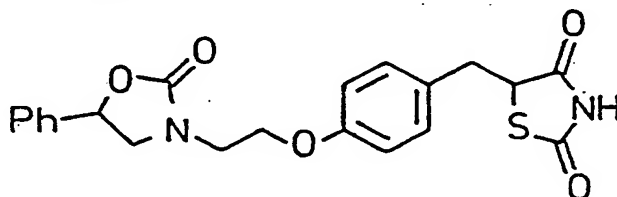
This spectrum is complicated by the presence of rotational isomers of the carbamate group.

25 2.80-4.30 (9H, complex; reduced to 8H on shaking with D_2O); 4.35 (1H, dd); 4.95 (1H, apparent broad singlet); 5.15 (2H, br s); 6.00 (1H, broad, exchanges with D_2O); and 6.70-7.40 (14H, complex).

Example 10

30 5-(4-[2-(5-Phenyl-2-oxazolidinon-3-yl)ethoxy]benzyl)-2,4-thiazolidinedione.

35



- 37 -

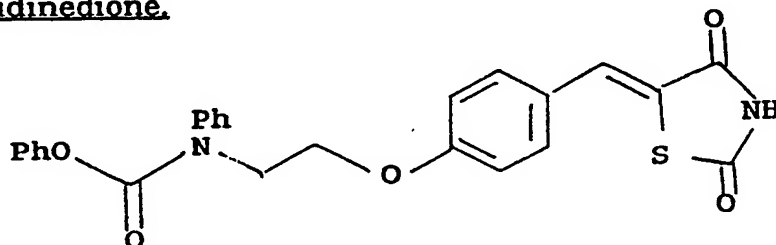
5-(4-[2-(N-Benzoyloxycarbonyl-N-(2-hydroxy-2-phenyl-ethyl)amino)-ethoxy]benzyl)-2,4-thiazolidinedione (5g) was dissolved in a mixture of ethanol (50ml) and dilute HCl (6M, 50ml) and heated at reflux for 4 hours. The solvent was evaporated and the pH of the residue adjusted to pH 6.5 with saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate (3x75ml), and the combined ethyl acetate layers dried (MgSO₄) and evaporated. Chromatography on silica gel with 5% methanol in dichloromethane as solvent afforded the title compound as a foam, mp 72-6°C.

¹H NMR δ (CDCl₃)

3.11 (1H, dd); 3.43 (1H, dd); 3.55-3.80 and 4.15 (combined 6H, complex); 4.48 (1H, dd); 5.50 (1H, dd); 6.81 (2H, d); 7.14 (2H, d); and 7.36 (6H, complex; reduced to 5H on shaking with D₂O).

Example 11

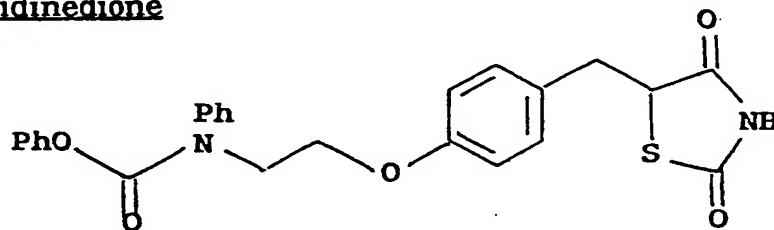
5-[4-[2-(N-Phenoxycarbonyl-N-phenylamino)ethoxy]benzylidene]-2,4-thiazolidinedione.



The title compound, mp 187-9°C, was prepared from 4-[2-(N-phenoxycarbonyl-N-phenylamino)ethoxy]benzaldehyde (3.67g) by a manner analogous to that described in Example 6.

¹H NMR δ (CDCl₃ /DMSO-d₆, 1:1)

4.20 (4H, complex); 6.95-7.60 (14H, complex); 7.70 (1H, s); and 12.22 (1H, br s, exchanges with D₂O).

Example 12**5-[4-[2-(N-Phenoxycarbonyl-N-phenylamino)ethoxy]benzylidene]-2,4-thiazolidinedione**

5-[4-[2-(N-Phenoxycarbonyl-N-phenylamino)ethoxy]benzylidene]-2,4-thiazolidinedione (3.93g) was hydrogenated in a manner similar to that described in Example 7 for a total of 98 hours at room temperature and pressure. The title compound, a foam mp 55-60°C, was obtained after chromatography of the crude product on silica gel with 1.5% methanol in dichloromethane as solvent.

 ^1H NMR δ (DMSO- d_6 ; 120°C)

- 20 This spectrum is complicated by rational isomers of the carbamate group. These coalesce at 120°C. 3.05 (1H, dd); 3.31 (1H, dd); 4.07 (2H, t); 4.17 (2H, t); 4.75 (1H, dd); 6.81 (2H, d); 7.05-7.45 (12H, complex) and 11.53 (1H, br s, exchanges with D_2O .)

DEMONSTRATION OF EFFICACY OF COMPOUNDSObese Mice. Oral Glucose Tolerance Test.

- 5 C57bl/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3 g/kg). Blood samples for glucose analysis were
- 10 taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control groups. 7 mice were used for each treatment.

<u>EXAMPLE NO:</u>	<u>LEVEL IN</u>	<u>%REDUCTION IN AREA</u>
	<u>DIET</u> <u>($\mu\text{mol kg}^{-1}$ of</u>	<u>UNDER BLOOD GLUCOSE</u>
	<u>DIET)</u>	<u>CURVE</u>
1	300	53
3	300	33
5	300	39
7	100	14
10	300	34
12	100	24

15

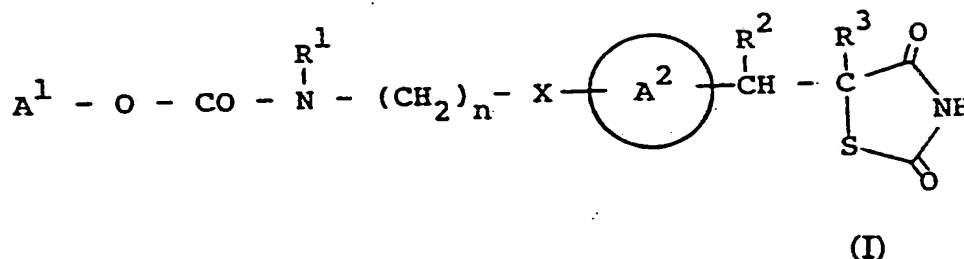
Toxicology

No toxicological effects were indicated for any of the compounds of the invention in any of the abovementioned tests.

20

Claims

1. A compound of formula (I):



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

15 A^1 represents an alkyl group, a substituted or unsubstituted aryl group or an aralkyl group wherein the alkylene or the aryl moiety may be substituted or unsubstituted;

A^2 represents a benzene ring having in total up to three optional substituents;

20 R^1 represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the alkyl or the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

or A^1 together with R^1 represents substituted or unsubstituted C₂₋₃ polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

25 R^2 and R^3 each represent hydrogen, or R^2 and R^3 together represent a bond;

X represents O or S; and

30 n represents an integer in the range of from 2 to 6.

2. A compound according to claim 1, wherein A^1 together with R^1 represents substituted or unsubstituted C₂₋₃ polymethylene group, optional substituents for the polymethylene group being selected from alkyl or aryl or adjacent substituents together with the methylene carbon atoms to which they are attached form a substituted or unsubstituted phenylene group;

35

3. A compound according to claim 3, wherein the substituted or unsubstituted C₂₋₃-polymethylene groups include substituted or unsubstituted ethylene groups.

5 4. A compound according to any one of claims 1 to 3, wherein the substituted or unsubstituted C₂₋₃ polymethylene groups represented by A¹ together with R¹ include 1,2-phenylene and a moiety of formula:



5. A compound according to claim 1, selected from the list consisting of:

15 5-(4-[2-(N-phenoxy carbonyl-N-methylamino)ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-benzyloxycarbonyl-N-methylamino)ethoxy]-benzylidene)-2,4-thiazolidinedione;

20 5-(4-[2-(N-benzyloxycarbonyl-N-methylamino)ethoxy]-benzyl)-2,4-thiazolidinedione;

25 5-(4-[2-(N-(2-phenylethoxy)carbonyl-N-methylamino)-ethoxy]benzyl)-2,4-thiazolidinedione;

5-(4-[2-(N-(2-phenylethoxy)carbonyl-N-methylamino)ethoxy]benzyl)-2,4-thiazolidinedione Sodium salt;

30 5-(4-[2-(2-benzoxazolinon-3-yl)ethoxy]benzylidene)2,4-thiazolidinedione;

5-(4-[2-(2-benzoxazolinon-3-yl)ethoxy]benzyl)-2,4-thiazolidinedione;

35 5-(4-[2-(N-benzyloxycarbonyl-N-(2-hydroxy-2-phenyl-ethyl)amino)-ethoxy]benzylidene)-2,4-thiazolidinedione;

5-(4-[2-(N-benzyloxycarbonyl-N-(2-hydroxy-2-phenyl-ethyl)amino)-ethoxy]benzyl)-2,4-thiazolidinedione;

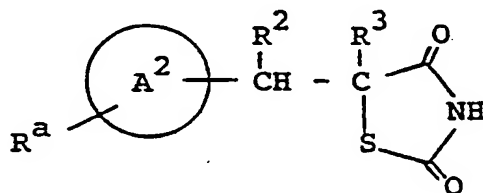
5-(4-[2-(5-phenyl-2-oxazolidinon-3-yl)ethoxy]benzyl)-2,4-thiazolidinedione.

5-[4-[2-(N-phenoxy carbonyl-N-phenylamino)ethoxy]benzylidene]-2,4-thiazolidinedione; and

5-[4-[2-(N-phenoxy carbonyl-N-phenylamino)ethoxy]benzyl]-2,4-thiazolidinedione; or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.

6. A process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, which process comprises:

a) reacting a compound of formula (II):



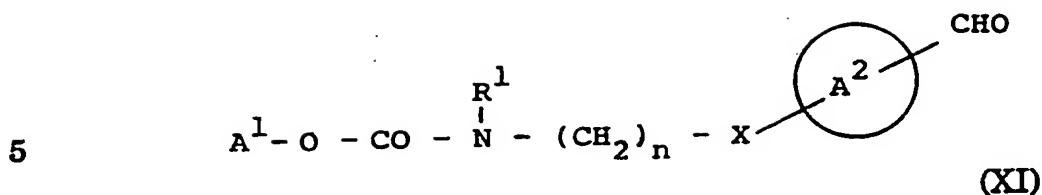
(II)

wherein R^2 , R^3 and A^2 are as defined in relation to formula (I), and R^a is a moiety convertible to a moiety of formula (b): or

$A^1-O-CO-NR^1-(CH_2)_n-X-$ (b)

wherein A^1 , R^1 , X and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (b):

b) by reacting a compound of formula (XI):



wherein R^1 , A^1 , A^2 , X and n are as defined in relation to formula (I) with 2,4-thiazolidinedione; and thereafter if required carrying out one or more
 10 of the following optional steps:

- (i) converting a compound of formula (I) into a further compound of formula (I);
 - 15 (ii) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.
7. A pharmaceutical composition comprising a compound of formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt
 20 thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.
8. A compound of formula (I), or tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically
 25 acceptable solvate thereof, for use as an active therapeutic substance.
9. A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically
 30 acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia, hypertension, cardiovascular disease and certain eating disorders.
10. A method for the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and certain eating
 35 disorders in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt

thereof and/or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

11. The use of a compound of formula (I), or a tautomeric form thereof
5 and/or a pharmaceutically acceptable salt thereof and/or a
pharmaceutically acceptable solvate thereof, for the manufacture of a
medicament for the treatment and/or prophylaxis of hyperglycaemia,
hyperlipidaemia, hypertension, cardiovascular disease and certain eating
disorders.

10

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/01834

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 D 277/34, A 61 K 31/425, C 07 D 417/12														
II. FIELDS SEARCHED <div style="text-align: right; margin-right: 100px;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 20%; border: none;">Classification System</td> <td style="border: none;">Classification Symbols</td> </tr> <tr> <td style="border: 1px solid black; height: 40px; vertical-align: bottom;">IPC5</td> <td style="border: 1px solid black; height: 40px; vertical-align: bottom;">C 07 D</td> </tr> </table> <div style="text-align: center; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div>			Classification System	Classification Symbols	IPC5	C 07 D								
Classification System	Classification Symbols													
IPC5	C 07 D													
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category[*]</th> <th style="width: 70%;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 20%;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>EP, A1, 0295828 (BEECHAM GROUP PLC) 21 December 1988, see the whole document ---</td> <td style="text-align: center; vertical-align: top;">1,5,6,7- 9,11</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A1, 0306228 (BEECHAM GROUP PLC) 8 March 1989, see the whole document ---</td> <td style="text-align: center; vertical-align: top;">1-9, 11</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A2, 0356214 (BEECHAM GROUP PLC) 28 February 1990, see the whole document -----</td> <td style="text-align: center; vertical-align: top;">1-9, 11</td> </tr> </tbody> </table>			Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	EP, A1, 0295828 (BEECHAM GROUP PLC) 21 December 1988, see the whole document ---	1,5,6,7- 9,11	A	EP, A1, 0306228 (BEECHAM GROUP PLC) 8 March 1989, see the whole document ---	1-9, 11	A	EP, A2, 0356214 (BEECHAM GROUP PLC) 28 February 1990, see the whole document -----	1-9, 11
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X	EP, A1, 0295828 (BEECHAM GROUP PLC) 21 December 1988, see the whole document ---	1,5,6,7- 9,11												
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A	EP, A2, 0356214 (BEECHAM GROUP PLC) 28 February 1990, see the whole document -----	1-9, 11												
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> Date of the Actual Completion of the International Search 17th January 1992 </td> <td style="width: 50%; border: none; vertical-align: top;"> Date of Mailing of this International Search Report 31. 01. 92 </td> </tr> <tr> <td style="width: 50%; border: none; vertical-align: top;"> International Searching Authority EUROPEAN PATENT OFFICE </td> <td style="width: 50%; border: none; vertical-align: top;"> Signature of Authorized Officer </td> </tr> </table>			Date of the Actual Completion of the International Search 17th January 1992	Date of Mailing of this International Search Report 31. 01. 92	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer 								
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International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer 													

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers...10..., because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims. It is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/01834

SA

52431

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/10/91. The European Patent office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0295828	21/12/88	JP-A-	1013076
		US-A-	4918091
EP-A1- 0306228	08/03/89	AU-D-	2173888
		JP-A-	1131169
		US-A-	5002953
EP-A2- 0356214	28/02/90	JP-A-	2083384

For more details about this annex: see Official Journal of the European patent Office, No. 12/82